SUMMARY MINUTES

OF THE

IMMUNOLOGY DEVICES PANEL MEETING

OPEN SESSION

December 13, 1999

Conference Room 020B
9200 Corporate Blvd.
Rockville, Maryland

Immunology Devices Panel Meeting

December 13, 1999

Panel Chairperson
Charles T. Ladoulis, M.D.

Executive Secretary
Louise E. Magruder

Voting Members
Betts Carpenter, M.D., Ph.D.
Glen L. Hortin, M.D., Ph.D.
Mary M. Kemeny, M.D.
Daniel P/ Petrylak, M.D.
Sheila E. Taube, Ph.D.

Temporary Voting Members
Donald A. Berry, Ph.D.
Robert R. DiLoreto, M.D.

Consumer Representative
Barnarese P. Wheatley, M.P.H.

Industry Representative
Erika B. Ammirati, R.A.C.

FDA Personnel

Nina Chace, M.S.
Scientific Reviewer

Murty Ponnapalli, Ph.D.
Statistician
DBS/OSB/CDRH

Peter E. Maxim, Ph.D.
Branch Chief
Immunology Branch
DCLD/ODE/CDRH

Jean Fourcroy, M.D.,Ph.D., M.P.H.
DCLD/ODR/CDRH

OPEN PUBLIC SESSION—December 13, 1999

Panel Chair Charles T. Ladoulis, M.D., called the session to order at 10:01 a.m. The panel members introduced themselves and noted their areas of expertise. Panel Executive Secretary Louise E. Magruder gave a brief summary of the November 9, 1998 meeting of the Immunology Devices Panel, at which the panel voted in favor of recommending for approval with conditions the premarket approval application (PMA) for the Vysis PathVysion Her-2 DNA Probe Kit to measure amplification of the Her-2 gene in patients with node positive, stage II breast cancer. She announced the tentative Immunology Devices Panel meeting dates for 20000 as March 17, June 16, September 15, and December 8.

Dr. Steve Gutman, director of the Division of Clinical and Laboratory Devices, recognized Drs. Kemeny, Taube, and Ladoulis for their service to the panel and presented them with a letter of appreciation and a plaque.

Dr. Thomas Gross, director of the Division of Postmarket Evaluation at CDRH, gave a presentation on postmarket surveillance and methods of postmarket evaluation at CDRH. He explained that medical devices have a definable life cycle, in which the clinical community has an important role to play in providing feedback during postmarket evaluation. He outlined the questions assessed in the postmarket period and described the Medical Device Reporting (MDR) Program, which provides limited but critical information to FDA about devices with problems, and he listed the possible actions prompted by such a medical device report. Dr. Gross discussed the two postmarket authorities, postmarketing surveillance and postapproval authority, and

outlined the criteria for a panel to suggest postmarketing surveillance as well as study designs used in postmarketing surveillance. He acknowledged the frustrations involved in monitoring the postmarketing period and challenged the advisory panel to ensure that a postmarketing study will be of primary importance, to specify the public health question it is to address, and to note what will be done with the data collected. He briefly outlined the future for the MDR and Postmarketing Surveillance programs.

Executive Secretary Louise Magruder stated that the purpose of the session was to discuss a premarket approval application (PMA) for an enzyme immunoassay (EIA) to be used as an aid in the diagnosis of patients with transitional cell carcinoma of the urinary tract. She read the conflict of interest statement and noted that no conflicts had been declared. Ms. Magruder also read appointments to temporary voting status for Drs. Berry and DiLoreto.

OPEN PUBLIC HEARING

Panel Chair Dr. Ladoulis invited public attendees to address the panel. There were no requests to speak.

PREMARKET APPROVAL APPLICATION FOR P940035 MATRITECH, INC.,'S NMP22 TEST KIT

Sponsor Presentation

Dr. Melodie R. Domurad introduced the PMA and summarized nonclinical data for the NMP22™ test kit, noting that the enzyme immunoassay had already been approved in July 1996 as an aid in management of patients with transitional cell carcinoma (TCC) of the bladder after surgical treatment to identify those patients with occult or rapidly recurring TCC. The sponsor was now applying for approval to use the

assay as an aid in diagnosis of persons with symptoms or risk factors for TCC. Dr. Domurad presented the results of an NCCLS precision study. She presented site-to-site reproducibility data and discussed concordance/discordance and regression analysis.

Dr. S. Bruce Malkowicz presented results from the clinical trial. He outlined the protocol, enrollment, and objectives, and he discussed patient selection, demographics, and baseline characteristics. Dr. Malkowicz presented median NMP22 values and percent distribution of NMP22 values in risk patients, healthy patients, persons with various benign diseases as well as other cancers. He explained the rationale for the choice of the diagnostic cutoff from pre-clinical trial physician evaluations. Safety studies showed that NMP22 is noninvasive, carries no risk of patient morbidity, and requires a single voided urine sample. There is no interference from hematuria. He stated that effectiveness studies showed that using a cutoff of 5U/mL, NMP22 is twice as sensitive as voided cytology to bladder carcinomas and more than twice as sensitive to early, noninvasive cancers and precancerous tumors. NMP22™ identified more invasive tumors than voided cytology and when used with cytology identified 100% of invasive tumors. NMP22™ detected a majority of the precancerous papillomas and is not dependent on visual morphological change. Dr. Malkowicz concluded that the NMP22 assay improves the potential for detection of early, more easily treatable tumors without increasing risk to the patient. He stated that prognosis of patients whose cancers are diagnosed at an earlier stage is better, and expenses are reduced due to less aggressive treatment and fewer surgeries for recurring and/or progressive tumors. He added that NMP22 is a safe and effective, low-cost adjunctive test, which can aid in the diagnosis of urinary tract tumors and has the potential to enhance the sensitivity of the standard evaluation.

Panel discussion after the sponsor presentation focused on issues involving anticipated use of the assay outside the intended use, i.e., evolution toward a screening tool, choice of the cutoff value, and application of the assay by untrained clinicians.

FDA Presentation

Nina Chace, M.S., Lead Scientific Reviewer, read the new intended use and previously approved intended use statements. She discussed previously approved and newly submitted nonclinical studies and listed four issues for panel consideration concerning the appropriate cutoff value as related to device performance characteristics as well as the possible creation of a physician brochure to discuss test performance at several different cutoffs.

Murty Ponnapalli, Ph.D., Statistician, presented the FDA's statistical analysis of the sponsor's site-to-site reproducibility study using two cutoff levels. Population overlap and assay imprecision were mentioned as two causes as two causes of false results. Using analysis of differences, regression, and concordant and discordant pairs, he showed results of tests for pairwise reproducibility and concluded that site to site reproducibility were poor by all methods of analysis. He also looked at various NMP22 cutoff values in terms of sensitivity, specificity, and positive and negative predictive value.

OPEN COMMITTEE DISCUSSION

Panel members commended the sponsors for the large clinical study, saying that this assay is a step forward and adds to the clinical armamentarium. They added that the major issue is to stress in labeling that the test is to be used in conjunction with, and not in lieu of current standard methods for evaluating high-risk patients. There was also

concern for the imprecision at lower NMP22 values and a suggestion to keep the cutoff level at a higher NMP22 value consistent with the calibrated value for the assay until further calibration and testing results are completed and submitted to the FDA in support of a lower cutoff value.

OPEN PUBLIC HEARING

There were no requests to address the panel from the audience.

There were no additional comments from the sponsors or the FDA.

The Panel Executive Secretary read the voting options to the panel.

A motion was made, seconded, and passed to recommend the PMA to the FDA as approvable with conditions. The conditions were as follows: 1) Labeling should state that the product is to be used in conjunction with, and not in lieu of current procedures and standard tests for diagnosing urinary tract cancer; and 2) The standard cutoff should be 7.5 units per mL, the lowest calibrated value used in the present studies, until the sponsor can provide different calibrators and data for the region of five U/mL or lower, which can then be submitted directly to the FDA. (An earlier motion was made and seconded to set the cutoff value at 10 units but failed to carry by a vote of four opposed and three in favor.)

On behalf of CDRH, the Executive Secretary thanked the panel, the sponsors, and the FDA staff. The meeting was adjourned at 3:20 p.m.

I certify that I attended the Meeting of the Immunology Devices Panel on December 13, 1999, and that this summary accurately reflects what transpired.

Louise E. Magruder
Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

Charles T. Ladoulis, M.D.
Panel Chair

Summary minutes prepared by
Aileen M. Moodie
9821 Hollow Glen Pl.
Silver Spring, MD 20910
301-587-9722